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# Single centre study of using bendamustine in the treatment of B-cell malignancies

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ORIGINAL ARTICLE

# Single centre study of using bendamustine in the treatment of B-cell malignancies

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## Abstract

**Objective:** To evaluate the experience of bendamustine in the treatment of B-cell malignancies at a tertiary care centre.

**Methods:** The retrospective descriptive analysis included data of all adult patients with B-cell malignancies treated with bendamustine from 2009 to 2011 at the Aga Khan University Hospital, Karachi. Data was analysed using SPSS 17.0. Frequencies and percentages were computed for baseline characteristics, responses and toxicities.

**Results:** Of the 19 patients 15 (79%) were males and 4 (21%) were females. The mean age was 59.53±12.14 (with a range of 46-86). Eight (42%) had follicular lymphoma, 6 (32%) had mantle cell lymphoma, 2 (11%) had diffuse large B-cell lymphoma, and 3 (16%) had chronic lymphocytic leukaemia. Four (21%) patients experienced grades 3 and 4 cutaneous toxicities. Eight (42%) patients were treated with bendamustine as first-line therapy. Six of them (75%) were included for response evaluation; 3 (50%) had complete response, and 3 (50%) had partial response. Eleven (58%) patients had relapsed disease out of which 3 (27.27%) had complete response, and 7 (63.63%) had partial response, whereas 1 (9%) had disease progression.

**Conclusion:** Bendamustine given as monotherapy or in combination is safe and useful in the treatment of patients with B-cell malignancies.


**Keywords:** Mantle cell lymphoma (MCL), Diffuse large B-cell lymphoma (DLBCL), Chronic lymphocytic leukaemia (CLL), Follicular lymphoma (FL), Complete remission (CR), Partial response (PR), Non-Hodgkin lymphoma (NHL). (JPMA 63: 702; 2013)

## Introduction

B-cell malignancies are a diverse group of neoplasm both in their natural history and response to treatment. They include non-Hodgkin's lymphoma (NHL) which is the most common haematological cancer and the sixth most common cancer in the United States, with an estimated 65,980 new cases and 19,500 deaths occurring in 2009.[1] There has been a dramatic increase in the incidence of NHL worldwide. Though well-characterised in the West,[2] in Karachi, Pakistan, NHL has been reported as the sixth most common malignancy in both genders with an incidence of 9.6/100,000 in males and 7.2/100,000 in females.[3] Overall institutional data reports a frequency of 6.1% for the city,[4] whereas a variation is apparently observed in the country as it has been reported as the most common cancer in Northern Pakistani males which may be due to the combination of environmental, infections and genetic factors.[5,6]

Treatment for indolent B-cell malignancies typically involves a combination of chemotherapy and immunotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab.[7] Alternatively, other chemotherapy regimens may be used in combination with rituximab, including cyclophosphamide, vincristine, and prednisone and fludarabine-based regimens. Radiation and bone marrow or stem cell transplantation are treatment options in selected patients. In developing countries like Pakistan and India, majority of the patients are treated with CHOP regimen with favourable response rates with only few patients receiving CD 20 (cluster of differentiation) therapy (rituximab), due to financial reasons.[6,8]

Bendamustine hydrochloride is an alkylating agent that has a unique, multifaceted mechanism of action. It produces double-stranded and single-stranded breaks in deoxyribonucleic acid (DNA), as do other alkylators. However, the DNA damage induced by bendamustine is more extensive and more durable than that produced by cyclophosphamide, melphalan or carmustine, indicating that bendamustine produces DNA damage by a mechanism distinct from that of other alkylators. Further, treatment with bendamustine impairs cell-cycle checkpoints by inducing a 60% to 80% down-regulation in the expression of several mitotic checkpoint genes, including polo-like kinase 1, aurora kinase A, and cyclin B1.[9] Defects in cell-cycle checkpoints, combined with

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DNA damage, can cause cells to enter mitosis before DNA repair has occurred. Cells that enter mitosis with significant DNA damage undergo a form of cell death known as mitotic catastrophe. When added to cells in culture, bendamustine induces mitotic catastrophe; this mechanism of inducing tumour cell death may be unique among alkylators.[10]

Bendamustine received marketing approval from the Food and Drug Administration in March 2008 for use as a first-line treatment of chronic lymphocytic leukaemia (CLL).[11] In October 2008, it was approved for the treatment of indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-based regimen.[12]

Generally, indolent NHL is incurable and follows a course of remission and relapses requiring multiple courses of chemotherapies with or without rituximab. Therefore, newer treatments are needed to prolong the duration of remission and overall survival in these patients.

The efficacy of bendamustine in the treatment of indolent NHL has been examined in several European and US trials.[9,13-16] It was also observed that this drug was generally well tolerated and had lower incidence of adverse effects when compared with CHOP plus rituximab regimen.[16] There is scarcity of data regarding the experience of bendamustine from our part of the region. The purpose of the current study was to share the experience with this novel agent in patients with B-cell malignancies.

## Patients and Methods

The study retrospectively reviewed the records of all patients with B-cell malignancies treated with bendamustine from 2009 to 2011 at the Aga Khan University Hospital, Karachi, Pakistan. Patients older than 18 years with World Health Organization (WHO) performance status $\leq$2 were eligible if they had histologically confirmed diagnosis of CLL, mantle cell lymphoma (MCL), follicular lymphoma (FL) (grades 1 to 2), and diffuse large B-cell lymphoma (DLBCL). All histopathologies of lymph node and bone marrow were reviewed at the Histopathology and Haematology Department. Patients were required to have at least one of the following criteria to demonstrate the need for treatment; impairment in haematopoiesis (haemoglobin <11 g/dl, white blood cells <1.5×10$^9$/L and platelets count <100×10$^9$), presence of 'B' symptoms, and other disease-related symptoms such as bulky disease or progressive disease.

All patients underwent pre-treatment evaluation, which included physical examination, routine complete blood count (CBC), serum chemistry evaluation, computed tomography (CT) chest scan, neck, chest, abdomen and pelvis, bone marrow aspiration, and trephine.

CT scans were used for response evaluation in line with literature.[17] Repeat pathology was done at progression of disease.

Bendamustine was administered at 90mg/m$^2$ or 120mg/m$^2$ a day for two days (30 min intravenous infusion).[14,18] Each cycle was repeated after 3 weeks as per protocol with or without rituximab. Rituximab was administered as intravenous infusion at a dose of 375mg/m$^2$ a day on the first day, followed by bendamustine on the second and third days to complete the cycle. Prophylactic antibiotics and growth factors were permitted depending on the patients' baseline characteristics.

Response evaluation was done after at least 4 courses of treatment received by each patient. However, responses were also assessed in those patients who received less than four courses and could not proceed with further courses because of cost issues or adverse effects, but had responded to the therapy. A complete remission (CR) was defined as the disappearance of all measurable disease (lymph node <1 cm) and return of normal counts. Normal counts were defined as haemoglobin>11 g/dl, white blood cell (WBC) >1.5 /mm$^3$ and platelets >100×10$^9$ /mm$^3$ and bone marrow showing no evidence of disease if present before the treatment. Partial response required more than 50% reduction of measurable disease and more than 50% improvement of all abnormal blood counts. Progression was defined as >25% increase in measurable disease with one of the following criteria, (1) corresponding enlargement of lymph node, liver or spleen; (2) appearance of new enlarged lymph nodes; (3) re-appearance or increasing infiltration of bone marrow; and (4) recurrence of B symptoms. Treatment toxicities were evaluated according to WHO grading criteria. CBC was performed weekly.

The data was retrieved through the hospital's registration system, and analysed using SPSS 17.0. Frequencies and percentages were computed for baseline characteristics, response, and toxicity to treatment.

## Results

A total of 19 patients including 15 (79%) males and 4 (21%) females, with a mean age of 59.53±12.14 years (range: 46-86 years), were part of the study. The mean age of males was 58±12.50 and that of females was 65.75±9.946 years. According to classification of histopathologies, 8 (42%) patients had FL, 6 (32%) had

Table-1: Patients' characteristics.

| Patients' characteristics | N (%) |
|---|---|
| Male | 15 (79%) |
| Mean age (years) | 59.53±12.14 (range 46-85) |
| **Histology** | |
| Follicular lymphoma | 8 (42%) |
| Mantle cell lymphoma | 6 (32%) |
| Diffuse large B-cell lymphoma | 2 (11%) |
| Chronic lymphocytic leukaemia | 3 (16%) |
| **Stage** | |
| I | 2 (11%) |
| II | 1 (05%) |
| III | 0 |
| IV | 16 (84%) |
| Performance status>2 | 0 |
| Abnormal LDH | 7 (39%) |
| Bone marrow involvement | 11 (58%) |
| Refractory to primary treatment | 11 (58%) |
| **Prior No. of treatments** | |
| 1 | 7 (64%) |
| 2 | 4 (36%) |
| Prognostic group for lymphoma patients | 16 |
| Low risk (1 risk factor) | 3 (19%) |
| Low intermediate risk (2 risk factor) | 2 (12%) |
| High intermediate (3 risk factor) | 8 (50%) |
| High risk (4-5 risk factor) | 3 (19%) |
| Prognostic group for follicular | 8 |
| Low risk (0-1 risk factor) | 2 (25%) |
| Intermediate risk (2 risk factor) | 0 |
| Poor risk (3-5 risk factor) | 6 (75%) |

Table-2: Evaluation response in patients treated with bendamustine.

| Entity | Complete remission | Partial remission | No response |
|---|---|---|---|
| FL (n=8) | 2 (25%) | 4 (50%) | 2 (25%) |
| MCL (n=6) | 4 (67%) | 2 (33%) | 0 |
| DLBCL(n=2) | 0 | 1 (50%) | 1 (50%) |
| CLL(n=3) | 0 | 3 (100%) | 0 |

FL: Follicular lymphoma; MCL: Mantle cell lymphoma; DLBCL: Diffuse Large B-cell Lymphoma; CLL: Chronic Lymphocytic Leukaemia.

Table-3: Evaluation of treatment-related toxicity.

| Adverse Effects | Grades | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Leucopenia | 14 | 3 | 1 | 0 | 1 |
| Thrombocytopenia | 8 | 2 | 3 | 4 | 2 |
| Anaemia | 13 | 1 | 4 | 1 | 0 |
| Nausea/vomiting | 13 | 4 | 2 | 1 | 0 |
| Allergic/skin reaction | 14 | 1 | 0 | 3 | 1 |
| Cardiotoxicity | 19 | 0 | 0 | 0 | 0 |
| Neurotoxicity | 18 | 1 | 0 | 0 | 0 |
| Alopecia | 19 | 0 | 0 | 0 | 0 |

MCL, 2 (11%) had DLBCL, and 3 (16%) had CLL. According to staging classification, 2 (11%) patients had stage I disease, 1 (5%) patient had stage II disease, and 16 (84%) had stage IV disease (Table-1).

Of the patients, 11 (58%) were treated for relapsed disease, of which 10 (90.90%) patients had stage IV disease. Prior treatment regimens included RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in 7 (36.84%) patients, RCVP (rituximab, cyclophosphamide, vincristine, prednisone) in 5 (26/31%) cases and ICE (ifosfamide, etoposide, carboplatin), hyper CVAD protocol (Hyperfractionated cydophosphamide, vincristine, doxorubicin and dexamethasone) and fludarabine base regimen in 1 (5/26%) patient each. Seven (36.84%) patients were treated with bendamustine as second-line and 4 (21%) patients were treated as third-line therapy.

In patients with lymphoma, according to International Prognostic Index (IPI), 5 (31%) were in low and low-intermediate prognostic index, and 11 (69%) were in high-intermediate and high-risk group. FL was also classified according to follicular lymphoma international prognostic index (FLIPI) in 8 (42%) patients; 6 (75%) had poor risk, while 2 (25%) patients had low risk.

In a total of 98 courses of bendamustine (range: 2-11), 13 (68.42%) patients received a dose of 90mg/m$^2$ and 6 (31.57%) patients received a dose of 120mg/m$^2$ in two consecutive days. Fourteen (73.68%) patients received rituximab along with bendamustine. The dose of bendamustine varied according to physicians' preference.

Eight (44%) patients were treated with bendamustine as first-line regimen. Six of them (75%) were included for response evaluation; 3 (50%) patients had complete response (CR) and 3 (50%) had partial response (PR). Two (25%) patients were still having treatment so they were not assessed for response. Eleven (58%) patients had relapsed disease. Of them 3 (27.27%) had CR and 7 (63.63%) had PR, while 1 (9%) patient had progression.

Six (31.57%) patients were with MCL; 4 (67%) had CR and 2 (33%) had PR. Eight (42%) patients were with FL; 2 (25%) had CR and 4 (50%) had PR while 2 (25%) patients were still receiving treatment and their evaluations were not done. One (50%) patient with DLBCL, and 3 (100%) with CLL had PR, whereas 1 (50%) patient with DLBCL had progression (Table-2).

A total of 98 treatment cycles were evaluated for toxicity (Table-3). Cutaneous grades 3 and 4 toxicities were experienced in four (21%) patients, of which 3 (75%) had generalised erythematous rash, and 1 (25%) had

reactivation of dermatomal herpes zoster during therapy, so the treatment was discontinued. Haematological toxicities were most frequently reported, with grades 3 and 4 thrombocytopenia in 6 (31%) patients, grade 3 anaemia in 1 (5.26%) patient, and grade 4 leucopenia in 1 (5.26%) patient. Non-haematologic toxicities were generally mild. Grades 1 and 2 nausea and vomiting were experienced in 7 (37%) patients. None of the patients experienced alopecia. There were no treatment-related deaths.

## Discussion

This report represents the first study regarding the experience of bendamustine in indolent B-cell malignancies in Pakistan. Majority of the patients in the population were of older age group as bendamustine has been observed to be well tolerated even in patients above 80 years of age with favourable responses and tolerability profile and, more so, the toxicity of bendamustine was low in this age group.[17]

Lymphoma with indolent histologies is often asymptomatic in the early stage and usually advanced at the time of detection. In the present study, 84% of the patients had stage IV disease and majority of them fell in high-risk category according to IPI. Bendamustine has been effective in refractory NHL. A recent US phase II trial of 76 patients with NHL treated with bendamustine had high objective response rates (ORR, 77% including 15% CR).[13] Another study observed the efficacy of bendamustine and rituximab in patients with relapsed indolent B-cell and MCL.[14] Eligible patients received up to three prior treatments; prior rituximab was allowed as long as the patients' disease was not refractory to rituximab. The ORR to treatment was 92%, including 41% CR.[14] Majority of the study's population had relapsed disease and all of them received rituximab as prior therapy, but were not refractory. The overall response rate was 91%, including 27% CR.

Majority of our patients had a relapsed and stage IV disease, yet the CR was much higher. This was because of the limited number of patients in our study. The results, as such, cannot be generalised. But this was an intriguing finding of excellent response which needs to be explored in prospective studies. We, as a population, are very diverse with different epigenetic factors and this could be an alternate explanation for this amazing response. However, these are only assumptions which need further confirmation. Our study can be considered as a preliminary report on the subject with detailed comprehensive ones to follow in the future.

As it was not a response evaluation study therefore patients were not matched stage-to-stage. The numbers were limited and the purpose was to share the experience and course of disease when treated with either bendamustine alone or with rituximab combination.

MCL generally experiences a more aggressive course, with rapid disease progression. Therapeutic options for this group are limited. Many patients quickly become refractory to treatment. In a recent retrospective study evaluating the efficacy of bendamustine in a small population of MCL treated with upfront bendamustine, patients had 60% CR and 40% PR.[14] Similarly, a large German phase III trial showed 66% ORR with 22% CR in one study and 94% ORR with 41% CR in another trial.[16,19] Fifty per cent of the study's MCL patients had refractory disease and most of them had advanced disease. CR was seen in 67% of the patients. One patient initially had PR with rituximab bendamustine after receiving 6 cycles, but after 9 months, had progression of disease. He was re-treated with the same regimen and had CR after 5 more cycles.

The efficacy and safety of bendamustine has been observed in the first-line setting in multiple studies.[15,21] The patients treated upfront with rituximab and bendamustine in one study had CR in 54% in a small population.[17] In this study, CR was observed in 3 patients, and PR in the other 3 patients.

Regarding the toxicity profile of bendamustine, most frequently observed were the severe cutaneous reactions, which is in line with literature.[21] These cutaneous reactions were treated by steroid and anti-histamine and they required dose reduction in the subsequent cycles. One patient discontinued treatment because of the re-activation of herpes zoster. She was treated with anti-viral and analgesics and eventually recovered. A similar case was also reported in a recent study.[22]

As with all other cytotoxic therapies, bendamustine suppresses bone marrow functions, commonly resulting in thrombocytopaenia, neutropaenia and anaemia. In this study population, grades 3 and 4 thrombocytopaenia was seen in 31% of the patients, as previously reported by other studies.[9,23] One patient was admitted with febrile neutropaenia, whereas another patient had grade 3 anaemia; these findings were consistent with literature.[22] The toxicity profile of rituximab and bendamustine is more beneficial in comparison with the combination of rituximab with CHOP-like therapy.[16] Treatment-related nausea and vomiting were generally mild and none of the patients had alopecia.

The objective of the current study was not to assess the tolerability or response; hence comparison with standard of care. It was only to share institutional experience in a

limited series of patients.

## Conclusion

Bendamustine given as monotherapy or in combination with rituximab is safe and useful in the treatment of patients with B-cell malignancies.

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